REMARKS

Claims 1, 3-35, 37-43, 50-54 and 61-66 were pending in the subject application. By this amendment, applicants have canceled claim 18 and amended claims 1 and 19-20. Accordingly, claims 1, 3-17, 19-35, 37-43, 50-54 and 61-66 are pending in the subject application.

Support for the amendment to claim 1 may be found *inter alia* on page 7, lines 28-33 of the subject application.

Support for the amendment to claim 19 may be found *inter alia* on page 7, lines 28-33 of the subject application.

Support for the amendment to claim 20 may be found *inter alia* on page 7, lines 28-33 of the subject application.

Previous Rejections

Applicants are pleased to learn that the rejections of claims 1, 3-35, 37-43, 50-54 and 61-66 over U.S Patent No. 6,214,791 to Arnon, et al., in view of the respective secondary references (i.e., U.S. Patent No. 6,024,981 to Khankari, et al.; U.S. Patent No. 5,965,600 to Sato, et al.; and U.S. Patent No. 6,162,800 to Dolle, et al.) have been withdraw.

Applicants, therefore, understand that the references to "the '981 patent" on page 3, first paragraph and on page 6, first paragraph of the November 17, 2004 Office Action are typographical errors. Furthermore, applicants assume for the purposes of this response that every reference by the Examiner to "the 981 patent" in the November 17, 2004 Office was intended to be a reference to U.S. Patent No. 5,075,115 to

Brine.

Double Patenting Over Arnon In View of Brine

On page 2, section 1 of the November 17, 2004 Office Action, the Examiner rejected claims 1, 3-35, 37-43, 50-54, 62-63 and 65 under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 7-14 of U.S. Patent No. 6,214,791 to Arnon et al ("Arnon") in view of U.S. Patent No. 5,075,115 to Brine ("Brine").

Specifically, the Examiner alleged that claims 7-11 of Arnon are drawn to the use of copolymer-1 for the manufacture of a medicament or pharmaceutical composition for the treatment of multiple sclerosis via ingestion or inhalation (7), wherein the medicament comprises 0.1-1000 mg of copolymer-1 (8), is formulated for oral or nasal administration (9), is administered via inhalation (10), or is enterically coated (11). The Examiner also alleged that claim 7 of Arnon is a genus claim which broadly encompasses the presently claimed method of making a copolymer-1 medicament (Instant claims 43 and 64-65) in light of the disclosure of Brine. The Examiner further alleged that claims 12-14 are drawn to a pharmaceutical composition for the treatment of multiple sclerosis via ingestion or inhalation (12), wherein the pharmaceutical composition is in solid, liquid, aerosol or inhalable powder form (13), or is enterically coated (14). The Examiner also alleged that claim 12 of Arnon is a genus claim which broadly encompasses the presently claimed pharmaceutical composition in light of the further disclosure of Arnon and the disclosure of Brine.

The Examiner alleged that the pharmaceutical composition

recited in claim 12 of Arnon comprises as an active ingredient a therapeutically effective amount of Copolymer 1(glatimer acetate). The Examiner alleged that as is evidenced by the disclosure of Arnon, the composition is used to treat multiple sclerosis by oral administration of copolymer-1 through ingestion, and that when copolymer-1 is introduced orally it may be in solid form, and it may be mixed with a pharmaceutically acceptable carrier. The Examiner also alleged that the disclosure of Arnon indicates that the use of enteric coatings is well known in the art, including methacrylic acid copolymer (Eudragit L; column 3, lines 27-42 in particular)(instant claims 18, 20,29-310. The Examiner further alleged that Arnon discloses that the administration of the composition orally, nasally or bronchially in liquid or solid form with a range of copolymer-1 from 0.1 to 1000 mg (column 2, line 45 to column 3, line 26) (instant claims 23-28, 32-42, 50-54, 62-63). The Examiner acknowledged that Arnon does not specifically recite that said carrier is microcrystalline cellulose in an amount in excess of 50% by weight or admixture with a lubricant but alleged that microcrystalline cellulose is well known in the art as a stable and physiologically inert excipient. The Examiner alleged that Brine teaches the formulation of pharmaceutical compositions as a controlled release dosage form. The Examiner also alleged that Brine teaches that the formulation of the invention may employ "[a]ny pharmaceutically active ingredient (column 3, lines 61-63 in particular). The Examiner further alleged that Brine teaches that an excipient may be employed in the formulation as a diluent, a binder, a lubricant, a disintegrant, an adsorbent or a combination of functions, that excipients are selected by the artisan "to provide their usual contribution" and "may be employed in an amount varying from 1% to about 90% by weight of

the dosage form" (column 5, lines 10-21 in particular) and that microcrystalline cellulose is "particularly desirable" as an excipient and is suitable as a binder, diluent and as a disintegrant. The Examiner also alleged that Brine teaches that microcrystalline cellulose is porous and can absorb a liquid medicament while remaining a free-flowing powder suitable as a feed formulation for compression and that Brine teaches in Examples 1 and 2 that release of active ingredient was more efficient when the percent-by-weight of the active ingredient was 25% and microcrystalline cellulose was 60% (Table III in particular) than when the percent-by-weight of the active ingredient was 60% and microcrystalline cellulose was 25% (Table II in particular). Finally, the Examiner alleged that Brine teaches the use of magnesium stearate as a lubricant in the feed formulation (column 6, lines 17-37 in particular)(instant claims 15-17). The Examiner included claims 34-35 because allegedly the use of preservatives in pharmaceutical formulations is well known to enhance the longevity of the formulation in storage.

The Examiner concluded that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to manufacture a composition comprising copolymer-1 as recited in claims 7-14 of Arnon using microcrystalline cellulose as an excipient and magnesium stearate as a lubricant as taught by Brine, and that one would have been motivated to combine these teachings using "in excess of 50% microcrystalline cellulose as an excipient" with a reasonable expectation of success by the teachings of Brine that microcrystalline cellulose can be used with any pharmaceutically active ingredient, is multifunctional as an excipient, has preferable properties for serving as a feed

formulation in the manufacture process, and the showing that "60% microcrystalline cellulose" by weight in the pharmaceutical composition yields more efficient release of the pharmaceutically active ingredient than 25% microcrystalline cellulose by weight.

Applicants' Reply

Arnon

Arnon relates to the treatment of multiple sclerosis by ingestion or inhalation of glatiramer acetate.

Brine

Brine is concerned with "a controlled and delayed release of active ingredient" (column 1, lines 13-14). According to Brine's Background of the Invention section, this goal is to be accomplished without the use of any sort of coating. According to Brine, using a coating to control release of the active ingredient is undesirable and characterized as a "disadvantage" (column 1, 23-34).

As an alternative to a coating, Brine discloses the use of a poly (lactic acid) matrix forming agent to control the release of the active ingredient (column 1, lines 9-14). The use of its poly (lactic acid) is a requirement of Brine (column 3, lines 28-43). However, the use of a given excipient is optional according to the Brine disclosure (column 3, lines 44-45).

Furthermore, Brine does not disclose "60% microcrystalline cellulose" ("MCC") as alleged by the Examiner. Brine does disclose "60% excipient" in its Example 2 (column 7, line 37). However, the term "excipient" clearly comprises other elements

besides MMC such as, for example, lubricant (column 6, lines 17-37). The precise amounts of MCC, lubricant and other things that constitute "60% excipient" are not described in Brine.

1. Motivation to combine Arnon and Brine is lacking

Turning to the Examiner's combination of Arnon and Brine, applicants note that MPEP § 2143.01 provides "three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art" citing *In re Rouffet,* 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998). MPEP § 2143.01 further provides that "[t]he level of skill in the art cannot be relied upon to provide the suggestion to combine references" citing *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999).

Applicants point out that Brine seeks to solve a completely different problem than that of the subject application. As noted above, Brine seeks to achieve the controlled and delayed release of an active ingredient from a pharmaceutical composition without the use of a coating. The potential active ingredients contemplated by Brine are small molecules (column 3, line 64 to column 4, line 24). On the other had, the subject invention is for a pharmaceutical composition comprising glatiramer acetate, a mixture of polypeptides which has a number of unique formulation concerns. Glatiramer acetate is a non-crystalline porous material that is only slightly soluble, has poor mixing and flow properties and is degraded by proteolytic enzymes (page 37, lines 17-23 of the subject application). Amended claim 1 of the subject application requires in excess of 50% by weight of microcrystalline cellulose and an enteric coating. Applicants'

amended claims recite features that specifically address the unique formulation problems associated with glatiramer acetate. Brine offers no teaching relevant to glatiramer acetae; Brine's concerns are simply different from those addressed by the subject invention.

Clearly, the teachings of the cited prior art provide no motivation for their combination. Brine does not teach the use of an enteric coating and in fact discourages the use of coatings. Brine does teach the use MCC but only in the presence of poly(lactiacid) and with a non-peptide active ingredient. Arnon teaches the use of glatiramer acetate and an enteric coating but provides no teaching of an amount of MCC in excess of 50% by weight. Therefore, in the absence of hindsight, there is nothing in Arnon or in Brine that would even remotely suggest their combination.

Accordingly, there is no motivation to combine Arnon and Brine.

2. Arnon and Brine are not combinable

MPEP § 2143.01 further provides that, "[I]f a proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification" *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984).

As noted above, Brine's pharmaceutical composition requires a poly (lactic acid) matrix forming agent with the purpose of avoiding the use of a coating. Applicants' amended claims require an enteric coating. The use of a coating with the

composition of Brine would render it unsatisfactory for its stated purpose. Stated otherwise, therefore, Brine and Arnon are not combinable.

3. Even if Arnon and Brine are combined, poly (lactic acid) can not be excluded

Even if despite any motivation but to explore hindsight, Arnon and Brine are combined, there is no rationale in either reference to exclude poly (lactic acid) from the combination. While Brine allows for alternative actives and excipients (column 6, lines 17-29), Brine requires poly(lactic acid) for all its compositions (column 3, lines 28-45). Therefore, poly(lactic acid) is an essential part of Brine and its teaching to use MCC is inseparable from the use of poly(lactic acid). Without the benefit of hindsight and the applicants' disclosure, the selection of in excess of 50% by weight MCC for use with glatiramer acetate would have been illogical.

4. Even if Arnon and Brine are combined, there is no expection of success

Even if despite any motivation but to explore hindsight, Brine and Arnon are combined, one skilled in the art would have had no expectation of successfully formulating glatiramer acetate. Whatever role MCC plays in the Brine composition has little relevance to a composition comprising of glatiramer acetate. The active ingredient exemplified in Brine is a small molecule. As noted above, glatiramer acetate is a mixture of polypeptides. Brine provides no guidance for the use of MCC with an active ingredient that is a polypeptide, a much larger molecule than those contemplated as active ingredients by Brine. This is in addition to the fact that Brine does not contemplate the effects of MCC in the absence of poly(lactic

acid) for any active ingredient.

Clearly, there is no teaching or suggestion in the any of the cited references that microcrystalline cellulose in excess of 50% would provide acceptable the advantageous dissolution characteristics of glatiramer acetate formulations.

5. Applicants' experimental results rebut a *prima facie* case of obviousness, even if there was one.

As discussed in the applicants' disclosure, the use of microcrystalline cellulose in excess of 50 % by weight results in pharmaceutical compositions with excellent flow and mixing characteristics, improved dissolution and improved stability over that which would have been expected based on the properties of glatiramer acetate (see page 37, lines 17-32 of the subject application). Based on the properties of glatiramer acetate, it was unexpected that the formulation with microcrystalline cellulose, particularly in excess of 50%, would have any, much less significantly improved pharmaceutical properties suitable for oral administration (see page 38, lines 1-13 of the subject application). For example, the claimed formulation has an advantageous property in that it allows for matching *in vitro* dissolution profiles of the tablet that contains 5 mg of glatiramer acetate with the tablet that contains 50 mg glatiramer acetate as shown in Figure 3. Specifically, and unexpectedly, even though the tablet containing 50 mg of glatiramer acetate is four times the weight of the tablet containing 5 mg of glatiramer acetate (see page 24, Table 5), both tablets have similar dissolution profiles (see page 37, line 29 to page 38, line 13). It is unexpected based on the prior art that the use of microcrystalline cellulose in excess of 50 % by weight will

provide such advantageous properties.

Claim 1, and claims dependent thereon, are patentable

For the each of the above reasons, independently discussed above, applicants respectfully submit that claim 1 and all claims dependent thereon of the subject application are patentable over Arnon in view of Brine.

Claim 3 recites additional patentable features

Claim 3 is dependent on claim 1 and further recites "wherein the amount of microcrystalline cellulose is at least 70 % by weight". Claim 3, like claim 1, is patentable over Arnon in view of Brine for the above reasons. In addition, claim 3 further distinguishes applicants' invention over Arnon and Brine, alone or in combination, because none of the cited references teach or suggest a pharmaceutical composition comprising glatiramer acetate, an amount of microcrystalline cellulose in excess of 70 % by weight and an enteric coating.

Claim 6 recites additional patentable features

Claim 6 is dependent on claim 1 and further recites "wherein the microcrystalline cellulose has a moisture content of up to 5.0%". Claim 6, like claim 1, is patentable over Arnon in view of Brine for the above reasons. In addition, claim 6 further distinguishes applicants' invention over Arnon and Brine, alone or in combination, because none of the cited references teach or suggest the use of MCC with a moisture content of up to 5.0%.

Claim 7 recites additional patentable features

Claim 7 is dependent on claim 1 and further recites "wherein the microcrystalline cellulose has a moisture content of up to

1.5%". Claim 7, like claim 1, is patentable over Arnon in view of Brine for the above reasons. In addition, claim 7 further distinguishes applicants' invention over Arnon and Brine, alone or in combination, because none of the cited references teach or suggest the use of MCC with a moisture content of up to 1.5%.

Claim 11 recites additional patentable features

Claim 11 is dependent on claim 1 through intervening dependent claims 8-10 and further recites with all the limitations of the intervening claims "the composition of claim 1 further comprising pregelatinized starch disintegrant with a moisture content of up to 14%". Claim 11, like claim 1, is patentable over Arnon in view of Brine for the above reasons. In addition, claim 11 further distinguishes applicants' invention over Arnon and Brine, alone or in combination, because none of the cited references teach or suggest the use of a pregelatinized starch disintegrant with a moisture content of up to 14%.

Claims 29-31 and 50-54 recites additional patentable features

Claim 29 and the claims which depend on it, i.e. claims 30-31 and 50-54, recite "a therapeutically effective amount of glatiramer acetate 70%-80% by weight of microcrystalline cellulose, and an enteric coating". Claims 29-31 and 50-54, like claim 1 are patentable over Arnon in view of Brine for the above reasons. In addition, claims 29-31 and 50-54 further distinguishes applicants' invention over Arnon and Brine, alone or in combination, because none of the cited references teach or suggest glatiramer acetate 70%-80% by weight of microcrystalline cellulose, and an enteric coating.

Double Patenting Over Arnon In View of Brine and Sato

On page 4, in section 2 of the November 17, 2004 Office Action, the Examiner rejected Claims 1, 20, 21, 22,43 and 64 under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 7-14 of Arnon in view of Brine and U.S. Patent No. 5,965,600 to Sato et al ("Sato").

In response, applicants point out that this rejection relies upon the improper and inoperative combination of Arnon and Brine. Therefore, this rejection fails for all of the reasons discussed above and should be withdrawn.

Double Patenting Over Arnon In View of Brine and Dolle

On page 5, in section 3 of the November 17, 2004 Office Action, the Examiner rejected that claims 1 and 61 under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 12-14 of Arnon in view of Brine and U.S. Patent No. 6,162,800 to Dolle et al ("Dolle").

In response, applicants point out that this rejection relies upon the improper and inoperative combination of Arnon and Brine. Therefore, this rejection fails for all of the reasons discussed above and should be withdrawn.

Double Patenting Over Arnon In View of Brine and Wizerkaniuk

On page 5, in section 4 of the November 17, 2004 Office Action, the Examiner rejected claims 43, 65 and 66 under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 7-11 Arnon in view of Brine and U.S. Patent No. 4,129,666 to

Wizerkaniuk ("Wizerkaniuk").

In response, applicants point out that this rejection relies upon the improper and inoperative combination of Arnon and Brine. Therefore, this rejection fails for all of the reasons discussed above and should be withdrawn.

For all of the above reasons, applicants respectfully request that the Examiner reconsider and withdraw the rejections set forth in the November 17, 2004 Office Action.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the $120.00 fee for the one-month extension of time is deemed necessary in connection with the filing of this Amendment. Accordingly, a check in the amount of $120.00 is enclosed. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Gary J. Gershik 3/16/05

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